1,015,396

PATENT SPECIFICATION

NO DRAWINGS

1,015,396

Date of Application and filing Complete Specification: Oct. 2, 1962.

No. 37319/62.

Application made in United States of America (No. 142,792) on Oct. 4, 1961.

Complete Specification Published: Dec. 31, 1965.

Index at acceptance:—C2 U(2, 3, 4A2, 4B1, 4B2, 4C4, 4C5, 4C9, 4X); C2 C(1E3K4, 1E3K6, 3A10E4C, 3A10E5F1C, 3A10E5F2A, 3A10E5F3A)

Int. Cl.:—C 07 c // C 07 d

COMPLETE SPECIFICATION

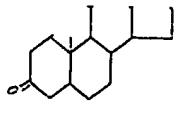
Steroid Compounds

ERRATA

SPECIFICATION No. 1,015,396
Amendment No. 1

Page 1, line 21, *for* "ammonia" *read* "ammonium"
Page 1, lines 53—54, *for* "gluccpyransoyl" *read* "glucopyranosyl"
Page 2, line 101, *for* "acid" *read* "acids"
Page 4, Expt. No. 12, *for* "16α" *read* "17α"
Page 6, line 56, *for* "-lucopyransid)" *read* "-glucopyransid)"
Page 10, line 105, *for* "pyrazale" *read* "pyrazalo"
Page 11, line 38, *for* "at" *read* "to"

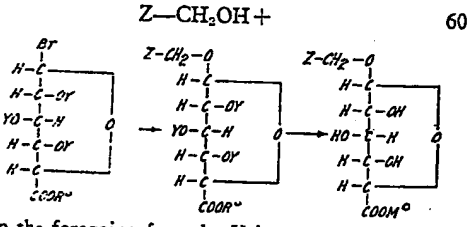
THE PATENT OFFICE
28th February 1966



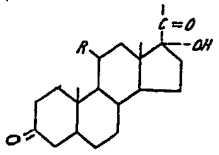
where R is keto or β-hydroxy and M is a hydrogen atom, an atom of an alkali metal, an equivalent of an alkaline-earth metal, or ammonia and choline, or basic amino acid, salts of these compounds in which M is hydrogen, which compounds contain a double bond in the 1 and/or 4 position with or without a double bond in the 6-position and optionally further substituted in Rings A, B, C and D of the steroid nucleus.

The invention is also concerned with the processes for preparing these glucuronide compounds and with pharmaceutical compositions containing them. These novel 21-glucuronides, while possessing the anti-inflammatory activity characteristic of cortisone, differ from cortisone, hydrocortisone, and their Δ¹-derivatives, prednisone and prednisolone, in being remarkably free from the ulcerogenic action, adrenal atrophy, thymus involution and body-weight-loss side-effects which have resulted

These reactions may be chemically represented as follows:



In the foregoing formula, Y is an acyl radical, R° is an alkyl or benzyl radical, M° is an atom of an alkali metal or an equivalent of an alkaline-earth metal, and Z- represents a steroid nucleus



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Int. Cl.:—C 07 c // C 07 d

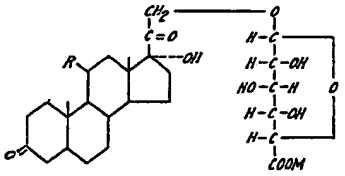
COMPLETE SPECIFICATION

Steroid Compounds

We, MERCK & Co. INC., a corporation duly organized and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned generally with novel steroid glucuronides and processes of preparing them.

The invention provides 21-glucuronide derivatives of steroids of the pregnane series having the formula:



where R is keto or β-hydroxy and M is a hydrogen atom, an atom of an alkali metal, an equivalent of an alkaline-earth metal, or ammonia and choline, or basic amino acid, salts of these compounds in which M is hydrogen, which compounds contain a double bond in the 1 and/or 4 position with or without a double bond in the 6-position and optionally further substituted in Rings A, B, C and D of the steroid nucleus.

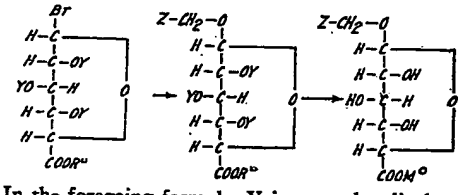
The invention is also concerned with the processes for preparing these glucuronide compounds and with pharmaceutical compositions containing them. These novel 21-glucuronides, while possessing the anti-inflammatory activity characteristic of cortisone, differ from cortisone, hydrocortisone, and their Δ^1-derivatives, prednisone and prednisolone, in being remarkably free from the ulcerogenic action, adrenal atrophy, thymus involution and body-weight-loss side-effects which have resulted from prolonged administration of the aforementioned anti-inflammatory steroids.

In accordance with the present invention the novel steroid 21-glucuronides are prepared by reacting the corresponding steroid 21-free alcohol compound with an alkyl or benzyl (tri-O - acyl - α - D - glucopyranosyl)bromide)-uronate to form the corresponding alkyl or benzyl (steroid - 21 - yl - tri - O - acyl - β-D - glucopyranosid) - uronate which is then reacted with an alkaline hydrolysing agent derived from an alkali metal or an alkaline-earth metal, thereby forming the corresponding salt of the steroid 21-glucuronide.

The steroid is preferably reacted with methyl (tri - O - acetyl - α - D - glucopyransoyl bromide) - uronate to form methyl (steroid - 21 - yl - tri - O - acetyl - β - D-glucopyranosid) - uronate which then is reacted with the alkaline hydrolysing agent.

These reactions may be chemically represented as follows:

$$Z\text{—}CH_2OH +$$



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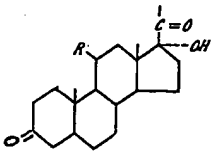

where R is as defined above and that contains